REMARKS

Amendments

Claims 1-9 and 12-17 have been amended to place the claims in accordance with U.S. patent practice. Claims 2-5 have been amended to remove the dependency of a multiple dependent claim on another multiple dependent claim. Additionally, exemplary embodiments have been deleted from claims 1-4, 6-8, and 14-16 and presented as new claims 18-28 as shown in the following table:

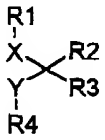
New Claim	Supported by exemplary embodiment(s) deleted from amended claim(s):	Support for new claim in specification
18	1-4	p. 2- p. 5
19-21	6	p. 10, l. 20 - p. 11, l. 5
22-23	7	p. 12, lines 11-17
24-25	8	p. 13, lines 1-15
26	14	p. 18, lines 7-11
27	15	p. 18, lines 7-11
28	16	p. 18, lines 7-11

Additionally, claims 19 and 21-25 recite the complete names of the compounds or chemical groups whose acronyms were used in original claims 6-8. A list of acronyms used in the application is found on pages 93-94 of the disclosure. Claims 10 and 11 have been canceled.

No new matter is introduced by any of the amendments herein.

Claims 1-9 and 12-17 -Version With Markings to Show Changes Made:

1. A compound of general Formula I



(I)

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein:

R_1 is selected from the group consisting of: [represents,]

C_1-C_6 alkyl, substituted with one or more basic groups [such as amino, amidino and/or guanidino];

cycloalkyl, substituted with one or more basic groups [such as amino, amidino and/or guanidino];

heterocyclyl, comprising [containing] at least one nitrogen atom;

heterocyclyl, comprising [containing] at least one hetero atom selected from S or O, and substituted with one or more basic groups [such as amino, amidino and/or guanidino]; and

[or] aryl, substituted with one or more basic groups; [such as amino, amidino and/or guanidino,]

R_2 is selected from the group consisting of [represents] H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O-, ZO-CO-NZ-, and [or] Z_2N-CO-NZ-; [group,]

R_3 is selectected from the group consisting of [represents] $COOR_5$, $SO(OR_5)$, SO_3R_5, $P{=}O(OR_5)_2$, $B(OR_5)_2$, $P{=}OR_5(OR_5)$, [or] tetrazole, and a [or any] carboxylic acid isostere; [.]

R_4 is [represents] SH, S-CO-C_1-C_6 alkyl, or S-CO-aryl; [,]

R_5 is [represents] H, C_1-C_6 alkyl, or aryl; [,]

R_6 is [represents] H or C_1-C_6 alkyl; [,]

X is selected from the group consisting of [represents] O, S, SO, SO_2, $C(Z)_2$, N(Z), NR_6SO_2, SO_2NR_6, NR_6CO, and [or] $CONR_6$; [,]

Y is [represents] $C(Z)_2$; and [,]

Z is [represents] independently selected from the group consisting of H, C_1-C_6 alkyl, aryl, cycloalkyl, and [or] heterocyclyl.

2. The compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein:

R_1 is selected from the group consisting of: [represents,]

cycloalkyl, substituted with one or more basic groups [such as amino, amidino and/or guanidino];

heterocyclyl, comprising [containing] at least one nitrogen atom;

heterocyclyl, comprising [containing] at least one hetero atom selected from S or O, and substituted with one or more basic groups [such as amino, amidino and/or guanidino]; and [or] aryl, substituted with one or more basic groups [such as amino, amidino and/or guanidino];

R_2 is selected from the group consisting of [represents] H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O-, ZO-CO-NZ-, and [or] Z_2N-CO-NZ-; [group,]

R_3 is [represents] $COOR_5$; [,]

R_4 is [represents] SH, S-CO-C_1-C_6 alkyl, or S-CO-aryl; [,]

R_5 is [represents] H, C_1-C_6 alkyl, or aryl; [,]

R_6 is [represents] H or C_1-C_6 alkyl; [,]

X is selected from the group consisting of [represents] O, S, SO, SO_2, $C(Z)_2$, N(Z), NR_6SO_2, SO_2NR_6, and [or] $CONR_6$; [,]

Y is [represents] $C(Z)_2$; and [,]

Z is [represents] independently selected from the group consisting of H, C_1-C_6 alkyl, aryl, cycloalkyl and [or] heterocyclyl.

3. The compound according to claim 1 [or 2], or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein:

R_1 is selected from the group consisting of: [represents,]

cycloalkyl, substituted with one or more basic groups [such as amino, amidino and/or guanidino];

heterocyclyl, comprising [containing] at least one nitrogen atom; and

heterocyclyl, comprising [containing] at least one hetero atom selected from S or O, and substituted with one or more basic groups [such as amino, amidino and/or guanidino];

R_2 is selected from the group consisting of [represents] H, C_1-C_3 alkyl, amino, halogen, and hydroxy; [,]

R_3 is [represents] $COOR_5$; [,]

R_4 is [represents] SH, S-CO-C_1-C_6 alkyl, or

S-CO-aryl; [,]

R_5 is [represents] H, C_1-C_6 alkyl, or aryl; [,]

X is [represents] $C(Z)_2$; [,]

Y is [represents] $C(Z)_2$; and [,]

Z is [represents] independently H or C_1-C_6 alkyl.

4. The compound according to claim 1 [any previous claim], or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein:

R_1 is selected from the group consisting of: [represents,]

cycloalkyl, substituted with one or more basic groups [such as amino, amidino and/or guanidino]; and

heterocyclyl, comprising [containing] at least one nitrogen atom;

R_2 is [represents] H, F, or C_1 alkyl; [,]

R_3 is [represents] $COOR_5$; [,]

R_4 is [represents] SH, S-CO-C_1-C_6 alkyl, or S-CO-aryl; [,]

R_5 is [represents] H, C_1-C_6 alkyl, or aryl; [,]

X is [represents] $C(Z)_2$; [,]

Y is [represents] $C(Z)_2$; and [,]

Z is [represents] independently H or C_1-C_6 alkyl.

5. The compound according to claim 1 [any previous claim], or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein:

R_1 is selected from the group consisting of [represents] cyclopentyl, pyridyl, pyrimidinyl, piperidinyl, and [or] thiazolyl; [,]

R_2 is [represents] H, F, or C_1 alkyl; [,]

R_3 is [represents] $COOR_5$; [,]

R_4 is [represents] SH; [,]

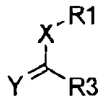
R_5 is [represents] H; [,]

X is [represents] CHZ; [,]

Y is [represents] CHZ; and [,]

Z is [represents] independently H or C_1-C_6 alkyl.

6. A process for the preparation of a compound according to any one of claims 1-5, wherein R_1, R_3, R_4, and Y are as defined in claim 1, [and] X is $C(Z)_2$, and R_2 is H, comprising the step of: [:]
reacting a compound of Formula VI,



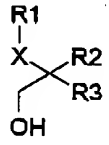
(VI)

wherein R_1, R_3 and Y are as defined in claim 1 and X is $C(Z)_2$, with a compound of Formula IX,

R5—SH (IX)

wherein R_5 is a [suitable] protecting group, optionally [such as Ac, Bz, PMB or Bn, alone or] in the presence of a [suitable] base [such as NaOMe, NaH or triethylamine] or [alternatively in the presence of] a free-radical initiator [, such as AIBN under standard conditions].

7. A process for the preparation of a compound according to any one of claims 1-5,
wherein R_1, R_2, R_3, and R_4 are as defined in claim 1, [and] Y is CH_2, and X is O, S, $C(Z)_2$, or N(Z), comprising the step of:
reacting a compound of Formula XIV,



(XIV)

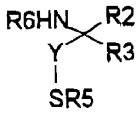
wherein R_1, R_2, and R_3 are as defined in claim 1, and X is O, S, $C(Z)_2$, or N(Z), with a compound of general Formula IX,

R5—SH (IX)

wherein R_5 is a [suitable] protecting group,[such as Ac or Bz,] in the presence of a [suitable] reagent, [such as PPh_3/DIAD,] under standard conditions.

8. A process for the preparation of a compound according to any one of claims 1-5, wherein R_1, R_2, R_3, R_4, and Y are as defined in claim 1, and X is NR_6CO [,] or NR_6SO_2, comprising the step of:

reacting a compound of [the] general Formula XV,



(XV)

wherein R_2, R_3, R_6 and Y are as defined in claim 1 and R_5 is a [suitable] protecting group, [such as Ac, Bz, PMB or Bn,] with a compound of [the] general Formula XVI,

(XVI)

wherein R_1 is as defined [for] in claim 1 and X is COOH or SO_2Cl, in the presence of a [suitable] coupling reagent [s, such as PyBOP/DIPEA, DCC/HOBt, EDC/TEA/DMAP or pyridine], under standard conditions.

9. A pharmaceutical formulation comprising [containing] a compound according to any one of claims 1 to 5 as active ingredient in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A method for treatment or prophylaxis of conditions associated with inhibition of carboxypeptidase U, comprising administering to a patient [mammal, including man,] in need of such treatment an effective amount of a compound according to [as defined in] any one of claims 1-5.

13. A pharmaceutical formulation for [use in] the treatment or prophylaxis of conditions associated with inhibition of carboxypeptidase U, comprising a compound according to [as

defined in] any one of claims 1-5 in combination with a pharmaceutically acceptable adjuvant, diluent, or carrier.

14. A pharmaceutical formulation, comprising:

(i) a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; [,] and

(ii) one or more antithrombotic agents with a different mechanism of action from that of component (i), [such as an antiplatelet agent, thromboxane receptor inhibitor, synthetase inhibitor, fibrinogen receptor antagonist, prostacyclin mimetic, phosphodiesterase inhibitor or ADP-receptor (P_2T) antagonist,]

in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier.

15. A kit of parts comprising:

(i) a pharmaceutical formulation comprising [containing] a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier; and

(ii) a pharmaceutical formulation comprising [containing] one or more antithrombotic agents with a different mechanism of action from that of component (i), [such as an antiplatelet agent, thromboxane receptor inhibitor, synthetase inhibitor, fibrinogen receptor antagonist, prostacyclin mimetic, phosphodiesterase inhibitor or ADP-receptor (P_2T) antagonist,]

in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier, [;]

wherein [which] compound (i) and agent (ii) are each formulated [provided in a form that is suitable] for administration in conjunction with the other.

16. A method for treatment of a patient suffering from, or susceptible to, a condition in which inhibition of carboxypeptidase U and a different antithrombotic mechanism are required or desired, which method comprises administering to the patient a therapeutically effective total amount of:

(i) a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier; and [in conjunction with]

(ii) one or more antithrombotic agents with a different mechanism of action from that of component (i), [such as an antiplatelet agent, thromboxane receptor inhibitor, synthetase inhibitor, fibrinogen receptor antagonist, prostacyclin mimetic, phosphodiesterase inhibitor or ADP-receptor (P_2T) antagonist,]

in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier.

17. A method for the treatment of a patient suffering from, or susceptible to, a condition in which inhibition of carboxypeptidase U and a different antithrombotic mechanism are required or desired, which method comprises administering to the patient the [a] formulation according to [as defined in] claim 14.

CONCLUSION

Upon entry of this Preliminary Amendment, claims 1-9 and 12-28 are pending. Applicants respectfully submit that claims 1-9 and 12-28 are directed to patentable subject matter. Accordingly, Applicant requests allowance of the claims.

Authorization is hereby given to charge any fee in connection with this communication to Deposit Account No. 23-1703.

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Respectfully submitted,

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